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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,216	07/11/2001	Jack R. Wands	21486-032DIV2	9747

30623 7590 09/29/2003

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/29/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,216	WANDS ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *16,39,42-44 and 46-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *16,39,42-44 and 46-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 17-22, 40, 41 and 45 have been canceled. Claim 57 has been added. Claims 16, 39, 42-44 and 46-57 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claims 42 and 43 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.. Claims 42 and 43 have been amended to recite dependency on amended claim 39. Claim 39 no specifically recites the embodiment that the antibodies must bind to an epitope within the catalytic domain of HAAH. The art recognizes that the FB50 antibodies of claims 42 and 43 bind an epitope of HAAH which is an extracellular epitope (Lavaissiere et al, cited in section 8 below). The art and the specification teach that that catalytic domain of HAAH is intracellular (specification , page 5, lines 19-22). Thus, the epitope bound by FB50 is not within the catalytic domain of HAAH which is cytoplasmic.

4. The rejection of claims 42 and 43 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record. New claim 57 is also rejected for the same reasons of record..

The specification fails to provide an enabling disclosure without complete evidence either that the claimed biological materials are know and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell lines producing the monoclonal antibodies designated as FB50, 86A, 5C7 and 19B. Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in

vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." Although the applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive an antibodies identical to FB50, 86A, 5C7 and 19B. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtained the claimed antibodies..

Although FB50 is known in the art through publication by a member of the instant inventive entity, the M.P.E.P. (2403) states:

> The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Thus, in order to satisfy the requirements of 35 U.S.C. 112, first paragraph, a deposit of FB50, 86A, 5CD7 and 19B is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be

replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridoma is producing the monoclonal antibody FB50, 86A, 5C7 and 19B as described in the specification as filed and is the same as that deposited in the depository, stating that the deposited hybridoma is producing the identical monoclonal antibody of FB50 as described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Applicant has amended the specification to incorporate the information that the hybridomas producing the FB-50, 86A, 5C7 and 19B were deposited under the terms of the Budapest Treaty, giving the address of the depository and stating that all availability to the public will be removed upon granting of a patent and that the hybridomas will be kept viable for the enforceable life of the patent and that applicants assignee acknowledges the duty to replace the sample in the event that the depository would be unable to furnish the sample when requested due to the condition of the deposit. However, it is noted that the hybridoma was deposited after the priority date of the instant application, and therefore a verified statement is required from a person in a position to corroborate that the deposited hybridoma is producing the monoclonal antibody FB50 as described in the specification as filed and is the same as that deposited in the depository, stating that the deposited hybridoma is producing the identical monoclonal antibody of FB50 as described in the specification and was in the applicant's possession at the time the application was filed. is required.

5. Claims 16, 44, 47-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16, 44, 51-56 are methods dependent upon the identity of a compound which inhibits "an enzymatic activity of HAAH", wherein said compound is dominant negative mutant of HAAH (SEQ ID NO:2) wherein said mutant comprises a mutation in the catalytic domain which comprises residues 650-700 of SEQ ID NO:2. Claims 47-50 are method claims dependent upon the identity of the dominant negative mutant of HAAH (SEQ ID NO:2), wherein said mutant comprises a substitution or deletion at residues 679 or 690 of SEQ ID NO:2). It is noted that the claim 16 recites "an enzymatic activity" and thus is not confined to hydroxylation activity. It is further noted that claims 16, 47 and 48 recite "wherein said mutant comprises".. When given the broadest reasonable interpretation the claims encompass mutants having mutations in regions outside of the catalytic domain for hydroxylation, and inhibiting enzymatic activities of HAAH beyond that of the disclosed hydroxylation activity. Thus the claims are dependent upon a genus of HAH mutants which include, but are not limited to mutants having substitutions or deletions within the catalytic domain for hydroxylation. The disclosure of mutants consisting of substitutions or deletions within residues of the hydroxylation domain (650-700) does not adequately describe other members of the genus because the other members would include mutants impacting other activities of HAAH which are not limited to hydroxylation and the specification has not disclosed other enzymatic activities of HAAH. Since the specification fails to adequately describe the product on which the claimed method is based it also fails to adequately describe the method.

Applicant states that the "allowability of claims 47 and 48 are acknowledged" however, claims 47 and 48 have been amended to recite "mutant comprising" over the former "mutant is" resulting in the rejection under 112, first above. Applicant argues on the top of page 10 that qualification of HAAH as SEQ ID NO:2 renders moot the prior rejection under 112, first paragraph, as lacking adequate written description. This has been considered but not found persuasive. It is noted in the prior grounds of rejection that the claims are not limited to specific

hydroxylation activity because the claims are drawn to the inhibition of "an enzymatic activity" rather than inhibition of hydroxylation (see page 11, lines 13 and 14 of section 13 of the previous Office action). The prior version of claims 47 and 48 were not included under these grounds of rejection because the prior claims read on a mutant consisting of a substitution or a deletion at residue 679 and 690, respectively, and said mutants would inherently be confined to a genus characterized by both structure and hydroxylation activity. The current version of the claims is a mutant "comprising" said deletions or substitutions and is thus much broader in scope than the prior version of claims 47 and 48. Claim 46 is not included under these grounds of rejection because the genus is confined structurally to a single mutant at position 675 which would inherently be devoid of hydroxylase activity.

6. Claims 16, 44, 46, 51, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al (U.S. 5,851,999) in view of Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231) and Korioth et al (Gene, 1994, Vol. 150, pp. 395-399) and Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001). Claim 16 is drawn to a method of inhibiting tumor growth in a mammal comprising administering to said mammal a compound which inhibits an enzymatic activity of HAAH, wherein said HAAH comprises SEQ ID NO:2, and wherein said compound is a dominant negative mutant of said HAAH, said mutant comprising a mutation in a catalytic domain of HAAH, said catalytic domain comprising residues 650-700 of SEQ ID NO:2. Claim 44is drawn. Claim 44 embodies the method of claim 16 wherein said mutation comprises a substitution or deletion of a histidine residue in said catalytic domain of HAAH. Claim 46 embodies the method of claim 16 wherein said mutation is a substitution or deletion at residues 675 of SEQ ID NO:2. Claim 51 embodies the method of claim 16 wherein said tumor is selected from the group consisting of colon, breast, pancreatic, liver or bile duct cancer. Claim 53 embodies the method of claim 16 wherein said tumor is a hepatocellular carcinoma. Claim 54 embodies the method of claim 16 wherein said tumor is a cholangiocarcinoma..

Ullrich et al teach a method of inhibiting tumor growth in a mammal comprising the administration of a dominant-negative mutant which binds to VEGF (column 5, lines 39-64, and column 19, line 25 to column 20, line 23). Ullrich et al teach the administration of

pharmaceutical compositions comprising FLK-1 receptor modulating compounds directly to the tumor as well a systemically (column 23, line 39 to column 24, line 15), thus fulfilling the specific embodiments of claims 49 and 50. Ullrich do not teach the administration of dominant negative mutants of HAAH or compounds which inhibit hydroxylation activity.

Lavaissiere et al teach that HAAH is responsible for an increase in hydroxylation activity in cancer cells which over express HAAH (Figure 7). Lavaissiere et al disclose that an epitope of HAAH is present in hepatocellular carcinoma and cholangiocarcinoma, breast and colon carcinomas (Table 1) thus fulfilling the specific embodiments of claims 51, 53 and 54 with respect to cancer of the liver, bile ducts, breast and colon. It is noted that although these teachings of Lavaissiere et al were set forth in the previous Office action, claims 51, 53 and 54 were indivertibly left out of the first sentence of the rejection. Lavaissiere et al teach that HAAH is responsible for an increase in hydroxylation activity in cancer cells which over express HAAH (Figure 7). Lavaissiere et al teach that it is necessary to establish whether the substantially increased activity of HAAH is merely associative or contributes to the generation and maintenance of the malignant phenotype (page 1322, last sentence).

Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231) identify the catalytic domain of bovine HAAH a consisting of a his-2 motif between residues 675 and 692 (Figure 2 of Jia et al). Korioth et al (Gene, 1994, Vol. 150, pp. 395-399) disclose the amino acid sequence for human HAAH and compared it to bovine HAAH (Figure 5 of Korioth et al). Korioth et al note that the C-terminal region consisting of residues 310-757 is highly conserved between bovine and human HAAH (page 398, first column, under the heading of "Comparison of the deduced sequences"). One can conclude by this comparison that the his-2 motif in human HAAH includes the same residues and thus the catalytic domain consists of residues 675 to 692 of human HAAH. Jia et al teach that when the his-675 residue was mutated to an alanine, no hydroxylation activity was detected in the resulting mutant. This residue corresponds to a histidine residue in human HAAH as evidenced by Korioth et al.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a the dominant negative mutant of HAAH by substitution the his-675 residue with alanine, and administer said mutant to a mammal to inhibit tumor growth. One of ordinary skill in the art would have been motivated to do so with a reasonable

expectation of success by the teachings of Jia et al and Korioth et al on the necessity for the His-675 residue for hydroxylation activity in HAAH and the suggestion of Lavaissiere et al on the need to establish the associative or casual nature of the increased hydroxylation activity by HAAH in carcinoma cells.

Applicant argues that Ulrich et al do not teach dominant negative mutant of VEGF, however, the truncated from of the receptor lacking most of the cytoplasmic domain would fulfill the embodiment of a dominant negative mutant as said protein would be incapable of signal transduction. Applicant further argues that the secondary references of Lavaissiere et al, Jia et al and Korioth et al describe the asparaginyl beta hydroxylases which are completely different proteins for the proteins of Ulrich et al as they differ both in structure and function. Applicant argues that none of the secondary references describe or suggest mutating HAAH in any way and that there is no suggestion to make a dominate negative mutant of HAAH must less a mutant containing a substitution with residues 650-700 of SEQ ID NO:2. this has been considered but not found persuasive. Jia et al teach the catalytic domain of bovine asparaginyl beta hydroxylase and the mutation rendering at residue 675 which rendered said protein devoid of hydroxylation activity.. Korioth et al teach that the C-terminal region of human asparaginyl beta hydroxylase is highly conserved with bovine asparaginyl beta hydroxylase. Thus is would be reasonable to conclude that the mutation of residue 675 in human asparaginyl beta hydroxylase would also rendered said enzyme unable to carry out hydroxylation. Lavaissiere et al teach that human asparaginyl beta hydroxylase is responsible for hydroxylation activity in cancer cells. Lavaissiere et al teach that it is necessary to establish whether the substantially increased activity of HAAH is merely associative or contributes to the generation and maintenance of the malignant phenotype. Ulrich et al teach the method wherein the overactivity of a protein can be overcome by the administration of mutants of said protein which are devoid of said activity.

Applicants argue that the limitation of the claims is that the catalytic domain be between residues 650 and 700 and that an analysis of the Korioth reference indicates that the domain is between residues 675 to 692 of human HAAH and therefore the rejection is moot. this has been considered but not found persuasive. Analysis of the Jia et al and Korioth et al references render obvious the fact that residue 675 of human asparginyl hydroxylase would have a catalytic histidine residue at position 675 and that substitution of said residue with alanine would render

the resulting protein devoid of hydroxylase activity. One of skill in the art would come to this conclusion because of the teachings of Jia et al that this histidine residue is crucial for hydroxylation activity in the bovine enzyme and according to the teachings of Korioth et al the C-terminus of the bovine and human enzymes are highly conserved. Regarding applicants arguments that there would be no suggestion to combine the teachings of Ulrich et al with the secondary references, it is noted that Lavaissiere et al teach the need to establish the associative or casual nature of the increased hydroxylation activity by HAAH in carcinoma cells. Ulrich et al teach the methodology wherein dominant negative mutant forms of proteins can inhibit the biological activity of the endogenous wild-type forms (column 5, lines 39-42). Ulrich et al that the dominant negative form of Flk-1 can be used for the treatment of diseases resulting from VEGF (the ligand of Flk-1) and/or Flk-1-mediated diseases such as cancer (column 5, lines 64). One of skill in the art would be motivated to substitute a dominant negative mutant of HAAH into the method of treating cancer as taught by Ulrich et al in order to use said dominant negative mutant as an antagonist of hydroxylation activity within the tumors taught by Lavaissiere et al, because Lavaissiere et al suggest that it is important to establish if the increased hydroxylation found within tumors as a result of the overactivity of HAAH is associative or casual. If administration of the dominant negative mutant of HAAH result in deceased tumor growth then it would be concluded that the association was casual. One of skill in the art would be motivated to determine this association in order to target HAAH in the treatment of tumors known to overexpress HAAH, i.e. liver, bile ducts, breast and colon as identified by Lavaissiere et al in Table 1.

7. Claims 39 and 57 are rejected 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting tumor growth in a mammal comprising the administration of an antibody conjugated to a chemotherapeutic agent which binds to an extracellular epitope of HAAH, or the FB-50 antibody conjugated to a cytotoxic agent, does not reasonably provide enablement for a method of inhibiting tumor growth in a mammal comprising the administration of an antibody which binds the intracellular catalytic domain of HAAH. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 16 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of a antibody or a fragment thereof which binds to an epitope within the catalytic domain of HAAH, said antibody being conjugated to a catalytic agent, wherein said domain comprises residues 650-700 of SEQ ID NO:2. Claim 57 is drawn to a method of inhibiting tumor growth in a mammal comprising administering to said mammal an antibody selected from the group consisting of FB-50, 5C7, 19B and 86A. It is noted that although the art teaches that the epitope for FB50 is accessible on the cell surface (page 1320, first column, lines 1-8 of Lavaissiere et al, Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323), and that the epitope is not within the catalytic domain of HAAH. Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231) identify the catalytic domain of bovine HAAH a consisting of a his-2 motif between residues 675 and 692 (Figure 2 of Jia et al). Korioth et al (Gene, 1994, Vol. 150, pp. 395-399) disclose the amino acid sequence for human HAAH and compared it to bovine HAAH (Figure 5 of Korioth et al). Korioth et al note that the C-terminal region consisting of residues 310-757 is highly conserved between bovine and human HAAH (page 398, first column, under the heading of "Comparison of the deduced sequences"). One can conclude by this comparison that the his-2 motif in human HAAH includes residues 678 to 695, and thus the catalytic domain consists of residues 678 to 695 of human HAAH.. Lavaissiere et al teach that the amino acid residues obtained by immunoscreening with the FB50 antibody are residues 146 to 183 (see Figure 4 and legend regarding the amino acids obtained by immunoscreening). Thus it can be concluded that FB50 does not bind to the catalytic domain of human HAAH. The specification teaches a number of monoclonal antibodies which are useful for binding to an epitope of the HAAH polypeptide (pg 2, lines 25-29) including the FB50 antibody.. The specification does not teach the immunogen used to raise the 5C7, 19B or 86A antibodies, nor does it teach if said antibodies bind intracellular or extracellular epitopes. The specification fails to teach how the intracellular epitopes of the catalytic domain are to be targeted by the claimed immunoconjugate. The specification contemplates intrabodies for binding to the cytoplasmic catalytic domain (page 5, lines 19-22, "An HAAH –specific intrabody is also useful to bind HAAH and inhibit intracellular HAZH enzymic activity by binding to an epitope in the catalytic domain of

HAAH"). However, for the reasons set forth in the previous Office action, the specification is not enabling for how to make said intrabody. Applicant states that the claims are now amended to exclude intrabodies, however, the specification provides not other teachings for how to target and antibody within the cytoplasmic domain. It is recognized in the art that samples may be treated with permeabilizing agents to allow for antibodies to permeate the cytoplasm and stain tissue samples (for example, Kerr and Thorpe, Immunochemistry LabFax, 1994, page 193). However, the instant claims are drawn to administering antibodies to a mammal and therefore, the procedures used to permeabilize cells to allow for antibody access to intracellular epitopes are not compatible with in vivo treatment. One of skill in the art would also have to establish if the antibodies of claim 57 bound to the extracellular or intracellular domains of HAAH because there is no way to deduce the epitope to which they bind by reading the specification. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use antibodies conjugated to cytotoxic agents that bound to the claimed cytoplasmic domain.

8. Claims 42, 43 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) in view of Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001).

It is noted that claims 42 and 43 are objected to for failing to further limit claim 39. Accordingly claims 42 and 43 will be read as independent claims comprising the specific embodiments of claim 39 with the exception of binding to an epitope of the catalytic domain. Thus claim 42 is drawn to a method of inhibiting tumor growth in a mammal comprising administering to said mammal the FB-50 antibody linked to a cytotoxic agent; and claim 43 is drawn to a method of inhibiting tumor growth in a mammal comprising administering an FB50 single chain molecule linked to a cytotoxic agent.. Claim 57 is drawn in part to a method of inhibiting growth in a mammal comprising administering to said mammal the FB50 antibody.

Schlom teaches a method for inhibiting tumor growth in a mammal comprising the administration of antibodies conjugated to chemotherapeutic drugs (page 107) or radio nuclides.

(page 108). Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30). Schlom does not teach antibodies which bind to HAAH, or antibodies which inhibit hydroxylation.

Lavaissiere et al disclose the monoclonal antibody FB-50 which binds to HAAH (page 1316, second column, under the heading "Molecular cloning of the antigen: its identification as HAAH"). Lavaissiere et al disclose that the epitope recognized by FB-50 is present on the surface of hepatocellular carcinoma and cholangiocarcinoma, breast and colon carcinomas (Table 1 and page 1320, first column, lines 1-5). Lavaissiere et al teach that HAAH is responsible for an increase in hydroxylation activity in cancer cells which over express HAAH (Figure 7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the FB50 antibody as taught by Lavaissiere et al in the general methods of inhibiting tumor growth in a mammal by the administration of antibodies and fragments thereof conjugated to chemotherapeutic agents or radio nuclides as taught by Schlom. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Lavaissiere et al on the expression of the FB50 epitope in hepatocellular carcinomas, cholangiocarcinomas, breast and colon cancers in contrast to its low expression in normal hepatocytes and non-neoplastic epithelial cells (abstract).. It would also be obvious to substitute the single chain FB-50 antibody in light of the teachings of Schlom on the advantages of advantages of using single chained antibodies over the parent murine antibodies for application in vivo.

Applicant argues that this rejection is now moot as the claims now have the specific embodiment of "an epitope with the catalytic domain of HAAH". However, for the reasons set forth in the objection to claim 42 and 43, the FB50 antibody does not bind to the catalytic domain and the dependence of claims 42 and 43 on claim 39 is improper.

9. All other rejections and objections as set forth in Paper No. 10 are withdrawn in light of applicants amendments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/26/03